UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,417	11/19/2003	Eivind Per Thor Straten	60820.000004	5850

21967 7590 03/23/2007

HUNTON & WILLIAMS LLP
INTELLECTUAL PROPERTY DEPARTMENT
1900 K STREET, N.W.
SUITE 1200
WASHINGTON, DC 20006-1109

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/715,417	STRATEN ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/21/04, 11/19/03, 12/21/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *8-13,18,19,29-31 and 41-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,14-17,20-28 and 32-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to Comply with the Sequence Rules.

DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Full compliance with the sequence rules is required in response to this Office Action. A complete response to this Office Action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with both these requirements in the time period set forth in this Office Action will be held non-responsive.

2. Applicants are required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 7 at lines 3-4 for motif peptide sequences with four defined amino acid residues).

3. Applicant's amendments filed 4/21/04 and 11/19/03 and Applicant's response filed 12/21/06 are acknowledged and have been entered.

4. Applicant's election with traverse of Group I (claims 1-40), and species of SEQ ID NO: 14 as the native human survivin peptide sequence and SEQ ID NO: 36 as the modified survivin peptide in Applicant's response filed 12/21/06 is acknowledged.

The basis for Applicant's traversal is of record in the said response on pages 14-15, briefly that examination of several of the restricted groups together would not constitute an undue burden, and that the species such as SEQ ID NO: 36, 27, 34 and 37 are related by homology.

Applicant's arguments have been fully considered, but are not persuasive.

It is the Examiner's position that:

There are two criteria for a proper requirement for restriction between patentably distinct inventions:

(1) The inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed (see MPEP 806.05 - 806.05(I)); and

(2) There must be a serious burden on the Examiner if restriction is not required (see MPEP 803.02 806.04(a) - (j), 808.01(a) and 808.02).

> Regarding undue burden, the M.P.E.P. 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search".

The inventions are distinct for reasons elaborated in paragraphs 4-10 of the previous Office Action.

Although Groups I and II share an assignment in Class 435, they do not share subclass assignments, therefore their classification is different.

Where the related inventions as claimed are shown to be independent or distinct under the criteria of MPEP 806.05(c)-806.06, the Examiner, in order to establish reasons for insisting upon restriction, must explain why there would be a serious burden on the Examiner if restriction is not required. Thus the Examiner must show by appropriate explanation one of the following:

A. Separate classification thereof: This shows that each invention has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Patents need not be cited to show separate classification.

B. A separate status in the art when they are classifiable together: Even though they are classified together, each invention can be shown to have formed a separate subject for inventive effort when the Examiner can show a recognition of separate inventive effort by inventors. Separate status in the art may be shown by citing patents that are evidence of such separate status, and also of a separate field of search.

C. A different field of search: Where it is necessary to search for one of the inventions in a manner that is not likely to result in finding art pertinent to the other inventions (*e.g.,* searching different classes/subclasses or electronic resources, or employing different search queries, a different field of search is shown, even though the two are classifiable together. The indicated different field of search must in fact be pertinent to the type of subject matter covered by the claims. Patents need not be cited to show different fields of search (see MPEP § 808.02).

Although the Invention of Group V shares a classification of the Invention of Group I, it is necessary to search the Invention of Group V in additional non-shared classifications, such as, for example, Class 424, subclasses 1.33, 1.37, 181.1, Class 514, subclasses 49 and 885.

With regard to Applicant's request for examination of a reasonable number of species, and homology between some peptide sequences, each peptide must be the subject of a separate sequence search against numerous protein databases.

Therefore, the restriction requirement enunciated in the previous Office Action meets this criterion of serious burden and therefore establishes that serious burden is placed on the Examiner by the examination of additional Groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 14-17, 20-28 and 33-40 read on the elected species, SEQ ID NO: 14 and 36.

Upon consideration of a search, since SEQ ID NO: 14 and 36 appear to be free of the prior art, the search has been extended to include SEQ ID NO: 1-5 recited in instant claim 7. Upon consideration of the art reference cited at item #20 of this Office Action below, the species of multiepitope vaccine recited in instant claim 32 has been included in examination.

Accordingly, claims 8-13, 18, 19 and 29-31 (non-elected species of Group I) and claims 41-49 (non-elected groups II-VII) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-7, 14-17, 20-28 and 32-40 are currently being examined.

5. The amendment filed 11/19/03 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the incorporation by reference to the parent applications. The amendment is not mentioned in the declaration or oath.

Applicant is required to cancel the new matter in the reply to this Office Action.

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware of in the specification.

8. The disclosure is objected to because of the following informalities:

a. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example, in the sentence spanning pages 37-38. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

b. The use of the trademarks PHOSPHORIMAGER, ALPHAIMAGER, MULTISCAN and LYMPHOPREP have been noted in this application at numerous locations, for example, on page 19 at line 24, page 24 at lines 37 and 26, and page 30 at line 31, respectively. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction(s) is/are required.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure.

The T2 cell line and the mAb W6/32 antibody are essential to the claimed invention. The reproduction of an identical cell line and mAb is an extremely unpredictable event. The cell line and mAb must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The instant specification does not disclose a repeatable process to obtain the cell line and mAb, and it is not apparent if the cell line and mAb are readily available to the public.

It is noted that the specification discloses that "[0023] The novel MHC Class I-restricted peptide of the invention is characterised by having at least one of several features, one of which is the ability to bind to the Class I HLA molecule to which it is restricted at an affinity, which, when it is measured by the amount of the peptide that is capable of half maximal recovery of the Class I HLA molecule (C.sub.50 value) in an assembly assay as described herein, is at the most 50 .mu.M. This assembly assay is carried out as described previously (12,13), and it is based on stabilisation of the HLA molecule after loading of peptide to the peptide transporter deficient cell line T2. Subsequently, correctly folded stable HLA heavy chains are immunoprecipitated using conformation dependent antibodies and the peptide binding is quantitated." The specification discloses at [0163] "Briefly, the assay is based on peptide-mediated stabilization of

empty HLA molecules released, upon cell lysis, from the TAP deficient cell line T2, stably transfected with HLA-B35 (kindly provided by Dr J. Haurum, Symphogen ApS, Lyngby, Denmark)." The specification does not disclose the method steps of the assembly assay except that stably folded HLA molecules were immunoprecipitated using mAb W6/32, and separated by IEF, then quantified using a phosphorimager program [0186].

If a deposit was made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicants, assignees or a statement by an attorney of record over his or her signature and registration number stating that the deposit has been made under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application is required.

If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(A) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(B) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(C) the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent whichever is longer;

(D) a viability statement in accordance with the provisions of 37 C.F.R. 1.807;

(E) the deposit will be replaced should it become necessary due to inviability, contamination, or loss of capability to function in the manner described in the specification.

Furthermore, unless the deposit was made at or before the time of filing, a declaration filed under 37 C.F.R. 1.132 is necessary to construct a chain of custody. Cell line or hybridoma producing mAb.... was deposited after the time of filing. The declaration, executed by a person in a position to know, should identify the deposited cell line or hybridoma producing mAb by its depository accession number, establish that the deposited plasmid is the same as that described in the specification, and establish that

the deposited plasmid was in Applicants possession at the time of filing. In re Lundak, 27 USPQ 90.

Biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The Office will accept commercial availability as evidence that a biological material is known and readily available only when the evidence is clear and convincing that the public has access to the material. A product could be commercially available but only at a price that effectively eliminates accessibility to those desiring to obtain a sample. The relationship between the applicant relying on a biological material and the commercial supplier is one factor that would be considered in determining whether the biological material was known and readily available. However, the mere fact that the biological material is commercially available only through the patent holder or the patent holder's agents or assigns shall not, by itself, justify a finding that the necessary material is not readily available, absent reason to believe that access to the biological material would later be improperly restricted.

11. Claims 1-6, 14-17, 20-28 and 32-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method

The instant claims encompass an MHC class I-restricted epitope peptide, pharmaceutical composition, vaccine and kit: (1) an MHC class I restricted epitope peptide that is "derived from any surivin", including that is a native sequence of survivin of a mammal species, including human, and including that is derived from human survivin by substituting, deleting or adding at least one amino acid residue, (2) an MHC class I restricted peptide that is capable of binding to an HLA class I molecule at the affinity recited in instant claim 1(i), but isn't immunogenic, (3) an MHC class I restricted peptide that is capable of binding to an HLA class I molecule, but isn't capable of *in situ* detection in a tumor tissue of CTLs that are reactive with the epitope peptide, (4) said peptide that has a *C50* value as recited in instant claim 1, 2 or 3, as determined by an assembly binding assay, but isn't immunogenic, *i.e.,* isn't an epitope, (5) said peptide *comprising* any of the amino acid residues indicated in the table recited in instant claim

20, that doesn't bind the indicated HLA class I molecule and/or is not immunogenic and may be of an unspecified length not suitable for MHC class I binding, (6) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at a frequency of at least 10 per 104 recited in instant claim 21, *i.e.,* of at least 1 per 10 PBLs (*i.e.,* at an extremely high frequency), (7) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient wherein CTL produced have cytotoxic effects against survivin expressing cells of a cancer cell line, including the two recited in instant claim 24, (8) a pharmaceutical composition comprising said peptide, including a composition comprising one having a subsequence of a native survivin and another that is a modified subsequence, and including wherein the peptides are SEQ ID NO: 36 and 14, (9) a vaccine composition comprising the said peptide, including wherein it is capable of eliciting an immune response against a cancer disease including wherein survivin is expressed, a multiepitope vaccine thereof, and including wherein the vaccine elicits the production *in vivo* of effector T cells having a cytotoxic effect against cancer cells, (10) the claimed kit comprising the peptide, and (11) the complex comprising the peptide, There is insufficient disclosure in the specification on such peptides, composition, vaccine, kit and complex thereof.

The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs)" ([0009]), and that "U.S. Pat. No. 6,245,523 discloses the isolation of purified survivin and it provides nucleic acid molecules that encode the survivin protein, and antibodies and other molecules that bind to survivin U.S. Pat. No. 6,245,523 also discloses anti-apoptotically active fragments of the survivin protein and variants hereof wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed survivin sequence. It is specifically disclosed that such peptides should contain key functional residues required for apoptosis, *i.e.,* Trp at position 67, Pro at position 73 and Cys at position 84" ([0011]). The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs). In a global gene expression analysis of about 4 million transcripts, survivin was identified as one of the top genes invariably up-regulated in many types of cancer but not in normal tissue (8)" [0009].

The specification does not disclose the sequence of survivin, nor does it incorporate by reference the disclosure of U.S. Pat. No. 6,245,523 into the instant specification, nor provide the sequence of any survivin from other mammalian or non-mammalian species. The specification describes *survivin* by the functional descriptor of being a member of the family of inhibitors of apoptosis proteins.

The specification further discloses that the peptides of the invention are derived from the known sequence of survivin, *e.g.,* the sequence disclosed in U.S. Pat. No. 6,245,523, and that the selection of peptides potentially having the ability to bind to a particular HLA molecule can be made by the alignment of known sequences that bind to a given particular HLA molecule to thereby reveal the predominance of a few related amino acids at particular positions in the peptides, *i.e.,* anchor residues ([0027]). The

specification discloses "a simple approach to identifying peptides of the invention includes the following steps: selecting a particular HLA molecule, e.g. one occurring at a high rate in a given population, carrying out an alignment analysis as described above to identify "anchor residue motifs" in the survivin protein, isolating or constructing peptides of a suitable size that comprise one or more of the identified anchor residues and testing the resulting peptides for (i) capability to bind to the particular HLA molecule using the assembly assay as described herein, (ii) the capability of the peptides to elicit INF-.gamma.-producing cells in a PBL population of a cancer patient at a frequency of at least 1 per 10.sup.4 PBLs as determined by an ELISPOT assay as described herein, and/or (iii) the capability of the peptides to detect in situ in a tumour tissue CTLs that are reactive with the epitope peptides being tested" ([0031]). Instant claim 20 recites a Table with a listing of some HLA class I molecules and their anchor residue positions and amino acid residues.

Evidentiary reference DiBrino *et al* (J. Immunol. 1993. 151(110: 5930-5935) teach "Taken together, our data are consistent with the view that anchor residue motifs for peptide binding to class I molecules will be useful for the identification of T cell epitopes, but in their simples form they will fail to identify all of the epitopes. The presence of anchor residues is not sufficient for binding, and some amino acids other than the most favorable anchor residues can be accommodated for peptide binding" (last paragraph of article).

Evidentiary reference Celis *et al* (Mol. Immunol. 1994. 31(18): 1423-1430) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens. Ochoa-Garay *et al* (Mol. Immunol. 1997. 34(1): 273-281) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin *et al* (J. Exp. Med. 1992, 180: 2227-2237) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. The claimed invention recites either a survivin peptide epitope or one that comprises a motif wherein residues not involved in MHC binding are not specified. Karin *et al* teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1). Thus Karin *et al* establish that amino acid residues not recited in the claimed peptide (*e.g.,* amino acid residues not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptides recited in the claims are immunogenic. Further, synthetic peptides

that are chosen on the basis of scanning the protein of interest for potential peptide sequences that have a motif for binding to an HLA molecule or molecules may not necessarily contain a T cell epitope, and therefore, may not induce a CTL response.

The specification discloses that "[0023] The novel MHC Class I-restricted peptide of the invention is characterised by having at least one of several features, one of which is the ability to bind to the Class I HLA molecule to which it is restricted at an affinity, which, when it is measured by the amount of the peptide that is capable of half maximal recovery of the Class I HLA molecule (C.sub.50 value) in an assembly assay as described herein, is at the most 50 .mu.M. This assembly assay is carried out as described previously (12,13), and it is based on stabilisation of the HLA molecule after loading of peptide to the peptide transporter deficient cell line T2. Subsequently, correctly folded stable HLA heavy chains are immunoprecipitated using conformation dependent antibodies and the peptide binding is quantitated." The specification discloses at [0163] "Briefly, the assay is based on peptide-mediated stabilization of empty HLA molecules released, upon cell lysis, from the TAP deficient cell line T2, stably transfected with HLA-B35 (kindly provided by Dr J. Haurum, Symphogen ApS, Lyngby, Denmark)."

The specification does not disclose the method steps of the assembly assay except that stably folded HLA molecules were immunoprecipitated using mAb W6/32, and separated by IEF, then quantified using a phosphorimager program [0186].

The specification discloses that some nonamer and decamer peptides that are subsequences of human survivin or substitution variants of said peptides can bind to selected HLA class I molecules (especially Table 4). The specification discloses that five stage IV melanoma patients were vaccinated with the modified HLA-A2 restricted sur1M2 peptide (SEQ ID NO: 5) loaded onto autologous dendritic cells, resulting in a strong T cell response to said peptide, and the detection of infiltration of survivin reactive cells into visceral and soft tissue metastases using *in situ* peptide/HLA-A2 multimer staining (page 44 at lines 4-11). The specification discloses that SEQ ID NO; 1, 2, 3, 4 and 5 bind to HLA-A2 with *C50* of 30, 30, 10, 1 and 1 uM, respectively, and that CTL or TIL from some CLL or melanoma patients could recognize or cross-react with complexes of the SEQ ID NO: 3 or 5 and HLA-A2 (especially Table 1). The specification discloses injection of dendritic cell loaded SEQ ID NO: 10 or 3 into cancer patients, and demonstration of induction of HLA-A2/SEQ ID NO: 10-specific T cells with the capacity to home to soft tissue and visceral metastases (especially pages 44-48), but does not disclose the relevance of the treatment with the clinical outcome observed, *i.e.,* how the composition or vaccine comprising the peptides treat or prevent cancer.

Evidentiary reference Matthias *et al* (Blood. 2005, 106(11), part 2, pp 369B, abstract 3 5145) teach that while a survivin peptide specific CTL could be detected in individuals with multiple myeloma, those same CTL were detected in 5% of healthy individuals.

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (e.g., by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Therapy. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Morel *et al* (Immunity 12: 107-117, 2000) teach the treatment of target cells for at least one week with IFN-γ to induce immunoproteasome expression in said target cells, and further teach that a number of antigenic peptides that are efficiently produced by the standard proteasome are not produced by the immunoproteasome. Morel *et al* further teach that a major difference between the two forms of proteasomes in terms of catalytic activity is the severely reduced ability of the immunoproteasome to cleave after acidic residues and also after residues with branched side chains; such as valine (paragraph spanning pages 113-114). Morel *et al* teach that an IFN-γ rich environment such as that found in a lymph node or a tumor mass heavily infiltrated with T cells could cause a proteasome switch in the tumor cells resulting in a lack of presentation of certain tumor antigens and escape from CTL attack (especially first sentence of the third full paragraph at column 1 on page 114).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that they have demonstrated the existence of T cell responses against two survivin deduced epitopes in cancer patients, and "However, at this time we do not know whether *survivin* peptides are actually presented by the tumor cells in vivo, because the formal proof for this notion is still lacking" (last paragraph of article).

Evidentiary reference Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) teach that "The ELISPOT methodology represents a strong tool to monitor peptide-specific T-cell response. However, although it has been shown that ELISPOT reactivity in most cases correlates with the capacity to lyse the target cell, the formal proof for this notion can be given only directly" (page 5966 at column 2, lines 3-7).

The specification discloses that SEQ ID NO: 36 recited in the pharmaceutical composition of instant claim 27 does bind HLA-A1 with a *C50* of 1 uM, but does not disclose if the peptide is immunogenic, and does not disclose that the second peptide in the said pharmaceutical composition SEQ ID NO: 14 binds any HLA class I molecule or is immunogenic (especially Table 4). The disclosed use of a pharmaceutical composition of the invention is to treat cancer ([0022]).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that the peptide STFKNWPFL (that is SEQ ID NO: 14 of instant claim 27) does not bind HLA-A2 (especially Table 1), thus indicating that the said peptide would not be useful in a pharmaceutical composition.

Evidentiary reference Reker *et al* (Cancer Biol. & Therapy. 2004, 3(2): 173-179) teach "To date, it is not known whether survivin is indeed a tumor rejection antigen, i.e., a tumor-associated antigen that can elicit immune responses in patients, which significantly impacts tumor growth... Thus if efficient immunity can be successfully elicited in cancer patients, without the induction of severe autoimmunity, survivin clearly becomes a prime candidate for a widely applicable cancer vaccine" (last paragraph of article).

The specification does not disclose any peptide or composition thereof used prophylactically as a vaccine.

Evidentiary reference the Merck Manual teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

The art recognizes that in order to be used for generating an immunogenic response, *i.e.*, for it to be an epitope, and also hence by extension to be used for *ex vivo* or *in situ* diagnosis of survivin reactive T cells of a cancer patient, that the said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no written description in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim, including for human, mammalian, non-mammalian or derived from survivin, nor which amino acid residues confer the properties recited in instant claim 1(ii) and (iii). The instant claims are drawn to a peptide epitope, not to a method for determining which peptides are epitopes, and as such the description is an invitation to experiment. With the exception of the specific peptides identified by amino acid sequence in the specification that have been shown to be immunogenic, the skilled artisan cannot envision the detailed structure of the encompassed peptides that bind to an HLA class I molecule and induce an immune response, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. In the instant application, the amino acid itself or isolated peptide is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

The recitation of "MHC class I-restricted epitope peptide", "derived from survivin", "native sequence of a mammal species", "derived from human survivn", "derived from a native sequence of survivn" is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being a member of a family of inhibitors of apoptosis proteins. It does not specifically define any of the compounds that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. In addition, a definition by function does not suffice to define the genus because it is only an indication of what the property the compound has, and if one extends the analysis in the instant case, what the compound does (*i.e.*, it inhibits some apoptosis protein(s)), rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06. It is only a definition of a useful result rather than a definition of what achieves that result. Many such species may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (*i.e.,* nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein.

12. Claims 1-7, 14-17, 20-28 and 32-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 3 and 5, and kit and HLA-A2/complex or multimer complex thereof, does not reasonably provide enablement for the MHC class I restricted epitope peptides recited in the instant claims, including SEQ ID NO: 1, 2 and 4, and pharmaceutical composition thereof (including those comprising SEQ ID NO: 1-5), composition thereof, vaccine thereof (including SEQ ID NO: 1-5), HLA class I/peptide complex or multimer complex thereof, or kit thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The specification has not enabled the breadth of the claimed invention because the claims encompass an MHC class I-restricted epitope peptide, pharmaceutical composition, vaccine and kit: (1) an MHC class I restricted epitope peptide that is "derived from any surivin", including that is a native sequence of survivin of a mammal species, including human, and including that is derived from human survivin by substituting, deleting or adding at least one amino acid residue, (2) an MHC class I restricted peptide that is capable of binding to an HLA class I molecule at the affinity recited in instant claim 1(i), but isn't immunogenic, (3) an MHC class I restricted peptide that is capable of binding to an HLA class I molecule, but isn't capable of *in situ* detection in a tumor tissue of CTLs that are reactive with the epitope peptide, (4) said peptide that has a *C50* value as recited in instant claim 1, 2 or 3, as determined by an assembly binding assay, but isn't immunogenic, *i.e.,* isn't an epitope, (5) said peptide *comprising* any of the amino acid residues indicated in the table recited in instant claim 20, that doesn't bind the indicated HLA class I molecule and/or is not immunogenic and is of unspecified length unsuitable for binding MHC class I, (6) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at a frequency of at least 10 per 104 recited in instant claim 21, *i.e.,* of at least 1 per 10 PBLs (*i.e.,* at an extremely high frequency), (7) a peptide that is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient wherein CTL produced have cytotoxic effects against survivin expressing cells of a cancer cell line, including the two recited in instant claim 24, (8) a pharmaceutical composition comprising said peptide, including a composition comprising one having a subsequence of a native survivin and another that is a modified subsequence, and including wherein the peptides are SEQ ID NO: 36 and 14, (9) a vaccine composition comprising the said peptide, including wherein it is capable of eliciting an immune response against a cancer disease including wherein survivin is expressed, a multiepitope vaccine thereof, and including wherein the vaccine elicits the production *in vivo* of effector T cells having a cytotoxic effect against cancer cells, (10) the claimed kit comprising the peptide, and (11) the complex comprising the peptide, There is insufficient disclosure in the specification on such peptides, composition, vaccine, kit and complex thereof.

The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed invention can be made and/or used.

The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs)" ([0009]), and that "U.S. Pat. No. 6,245,523 discloses the isolation of purified survivin and it provides nucleic acid molecules that encode the survivin protein, and antibodies and other molecules that bind to survivin U.S. Pat. No. 6,245,523 also discloses anti-apoptotically active fragments of the survivin protein and variants hereof wherein an amino acid residue has been inserted N- or C-terminal to, or within, the disclosed survivin sequence. It is specifically disclosed that such peptides should contain key functional residues required for apoptosis, *i.e.,* Trp at position 67, Pro at position 73 and Cys at position 84" ([0011]). The specification discloses that "survivin is a recently identified member of the family of inhibitors of apoptosis proteins (IAPs). In a global gene expression analysis of about 4 million transcripts, survivin was identified as one of the top genes invariably up-regulated in many types of cancer but not in normal tissue (8)" [0009].

The specification does not disclose the sequence of survivin, nor does it incorporate by reference the disclosure of U.S. Pat. No. 6,245,523 into the instant specification, nor provide the sequence of any survivin from other mammalian or non-mammalian species. The specification describes *survivin* by the functional descriptor of being a member of the family of inhibitors of apoptosis proteins.

The specification further discloses that the peptides of the invention are derived from the known sequence of survivin, *e.g.,* the sequence disclosed in U.S. Pat. No. 6,245,523, and that the selection of peptides potentially having the ability to bind to a particular HLA molecule can be made by the alignment of known sequences that bind to a given particular HLA molecule to thereby reveal the predominance of a few related amino acids at particular positions in the peptides, *i.e.,* anchor residues ([0027]). The specification discloses "a simple approach to identifying peptides of the invention includes the following steps: selecting a particular HLA molecule, e.g. one occurring at a high rate in a given population, carrying out an alignment analysis as described above to identify "anchor residue motifs" in the survivin protein, isolating or constructing peptides of a suitable size that comprise one or more of the identified anchor residues and testing the resulting peptides for (i) capability to bind to the particular HLA molecule using the assembly assay as described herein, (ii) the capability of the peptides to elicit INF-.gamma.-producing cells in a PBL population of a cancer patient at a frequency of at least 1 per 10.sup.4 PBLs as determined by an ELISPOT assay as described herein, and/or (iii) the capability of the peptides to detect in situ in a tumour tissue CTLs that are reactive with the epitope peptides being tested" ([0031]). Instant claim 20 recites a Table with a listing of some HLA class I molecules and their anchor residue positions and amino acid residues.

Evidentiary reference DiBrino *et al* (J. Immunol. 1993. 151(110: 5930-5935) teach "Taken together, our data are consistent with the view that anchor residue motifs for peptide binding to class I molecules will be useful for the identification of T cell epitopes, but in their simples form they will fail to identify all of the epitopes. The presence of anchor residues is not sufficient for binding, and some amino acids other than the most favorable anchor residues can be accommodated for peptide binding" (last paragraph of article).

Celis *et al* (Mol. Immunol. 1994. 31(18): 1423-1430) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens. Ochoa-Garay *et al* (Mol. Immunol. 1997. 34(1): 273-281) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin *et al* (J. Exp. Med. 1992, 180: 2227-2237) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. The claimed invention recites either a survivin peptide epitope or one that comprises a motif wherein residues not involved in MHC binding are not specified. Karin *et al* teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1). Thus Karin *et al* establish that amino acid residues not recited in the claimed peptide (*e.g.,* amino acid residues not involved in MHC binding of a peptide) will play a pivotal role in determining whether the peptides recited in the claims are immunogenic. Further, synthetic peptides that are chosen on the basis of scanning the protein of interest for potential peptide sequences that have a motif for binding to an HLA molecule or molecules may not necessarily contain a T cell epitope, and therefore, may not induce a CTL response.

In addition, the art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27, Curr. Opin. Biol. 1994, 6: 13-23.) Thus, the amino acid residues at the peptides' termini make

a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10, Nature 1992, 360: 364-366.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27).

The specification discloses that "[0023] The novel MHC Class I-restricted peptide of the invention is characterised by having at least one of several features, one of which is the ability to bind to the Class I HLA molecule to which it is restricted at an affinity, which, when it is measured by the amount of the peptide that is capable of half maximal recovery of the Class I HLA molecule (C.sub.50 value) in an assembly assay as described herein, is at the most 50 .mu.M. This assembly assay is carried out as described previously (12,13), and it is based on stabilisation of the HLA molecule after loading of peptide to the peptide transporter deficient cell line T2. Subsequently, correctly folded stable HLA heavy chains are immunoprecipitated using conformation dependent antibodies and the peptide binding is quantitated." The specification discloses at [0163] "Briefly, the assay is based on peptide-mediated stabilization of empty HLA molecules released, upon cell lysis, from the TAP deficient cell line T2, stably transfected with HLA-B35 (kindly provided by Dr J. Haurum, Symphogen ApS, Lyngby, Denmark)."

The specification does not disclose the method steps of the assembly assay except that stably folded HLA molecules were immunoprecipitated using mAb W6/32, and separated by IEF, then quantified [0186].

The specification discloses that some nonamer and decamer peptides that are subsequences of human survivin or substitution variants of said peptides can bind to selected HLA class I molecules (especially Table 4). The specification discloses that five stage IV melanoma patients were vaccinated with the modified HLA-A2 restricted sur1M2 peptide (SEQ ID NO: 5) loaded onto autologous dendritic cells, resulting in a strong T cell response to said peptide, and the detection of infiltration of survivin reactive cells into visceral and soft tissue metastases using *in situ* peptide/HLA-A2 multimer staining (page 44 at lines 4-11). The specification discloses that SEQ ID NO; 1, 2, 3, 4 and 5 bind to HLA-A2 with *C50* of 30, 30, 10, 1 and 1 uM, respectively, and that CTL or TIL from some CLL or melanoma patients could recognize or cross-react with complexes of SEQ ID NO: 3 or 5 and HLA-A2 (especially Table 1). The specification discloses injection of dendritic cell loaded SEQ ID NO: 10 or 3 into cancer patients, and demonstration of induction of HLA-A2/SEQ ID NO: 10-specific T cells with the capacity to home to soft tissue and visceral metastases (especially pages 44-48), but does not disclose the relevance of the treatment with the clinical outcome observed, *i.e.,* how the composition or vaccine comprising the peptides treat or prevent cancer.

Evidentiary reference Matthias *et al* (Blood. 2005, 106(11), part 2, pp 369B, abstract 3 5145) teach that a survivin peptide specific CTL could be detected in individuals with multiple myeloma, those same CTL were detected in 5% of healthy individuals.

Evidentiary reference Celis (J. Clin. Invest. 2002, 110(12: 1765-1768) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (e.g., by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Therapy. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Morel *et al* (Immunity 12: 107-117, 2000) teach the treatment of target cells for at least one week with IFN-γ to induce immunoproteasome expression in said target cells, and further teach that a number of antigenic peptides that are efficiently produced by the standard proteasome are not produced by the immunoproteasome. Morel *et al* further teach that a major difference between the two forms of proteasomes in terms of catalytic activity is the severely reduced ability of the immunoproteasome to cleave after acidic residues and also after residues with branched side chains, such as valine (paragraph spanning pages 113-114). Morel *et al* teach that an IFN-γ rich environment such as that found in a lymph node or a tumor mass heavily infiltrated with T cells could cause a proteasome switch in the tumor cells resulting in a lack of presentation of certain tumor antigens and escape from CTL attack (especially first sentence of the third full paragraph at column 1 on page 114).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that they have demonstrated the existence of T cell responses against two survivin deduced epitopes in cancer patients, and "However, at this time we do not know whether *survivin* peptides are actually presented by the tumor cells in vivo, because the formal proof for this notion is still lacking" (last paragraph of article).

Evidentiary reference Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) teach that "The ELISPOT methodology represents a strong tool to monitor peptide-specific T-cell response. However, although it has been shown that ELISPOT reactivity in most cases correlates with the capacity to lyse the target cell, the formal proof for this notion can be given only directly" (page 5966 at column 2, lines 3-7).

The specification discloses that SEQ ID NO: 36 recited in the pharmaceutical composition of instant claim 27 does bind HLA-A1 with a *C50* of 1 uM, but does not disclose if the peptide is immunogenic, and does not disclose that the second peptide in the said pharmaceutical composition SEQ ID NO: 14 binds any HLA class I molecule or is immunogenic (especially Table 4). The disclosed use of a pharmaceutical composition of the invention is to treat cancer ([0022]).

Evidentiary reference Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) teach that the peptide STFKNWPFL (that is SEQ ID NO: 14 of instant claim 27) does not bind HLA-A2 (especially Table 1), thus indicating that the said peptide would not be useful in a pharmaceutical composition.

Evidentiary reference Reker *et al* (Cancer Biol. & Therapy. 2004, 3(2): 173-179) teach "To date, it is not known whether survivin is indeed a tumor rejection antigen, i.e., a tumor-associated antigen that can elicit immune responses in patients, which significantly impacts tumor growth...Thus if efficient immunity can be successfully elicited in cancer patients, without the induction of severe autoimmunity, survivin clearly becomes a prime candidate for a widely applicable cancer vaccine" (last paragraph of article).

The specification does not disclose any peptide or composition thereof used prophylactically as a vaccine.

Evidentiary reference the Merck Manual teaches that a vaccine is a suspension of whole or fractionated bacteria or viruses that have been rendered nonpathogenic and is given to induce an immune response and prevent subsequent disease.

Evidentiary reference Encyclopedia Brittanica Online defines vaccine as a suspension of weakened, killed, or fragmented microorganisms or toxins or of antibodies or lymphocytes that is administered primarily to prevent disease.

The art recognizes that in order to be used for generating an immunogenic response, *i.e.*, for it to be an epitope, and also hence by extension to be used for *ex vivo* or *in situ* diagnosis of survivin reactive T cells of a cancer patient, that the said peptide must bind MHC and also present an epitope recognized by T cells. The art recognizes that the T cell epitope differs from the amino acids pertinent to MHC binding. There is no disclosure in the specification of the amino acids that constitute the T cell epitope in the peptide recited in the claim, including for human, mammalian, non-mammalian or derived from survivin, nor which amino acid residues confer the properties recited in instant claim 1(ii) and (iii). The instant claims are drawn to a peptide epitope, not to a method for determining which peptides are epitopes, and as such the disclosure is an invitation to experiment, even when motif amino acid residues are recited for peptides that bind some HLA class I molecules. With the exception of the specific peptides identified by amino acid sequence in the specification that have been shown to be immunogenic, it is unpredictable which sequences from which undisclosed proteins designated as a "survivin" or designated as human survivin or mammalian survivin or derived from survivin or being a deletion, substitution or addition mutant of said sequence will bind to an HLA class I molecule and induce an immune response.

It is unpredictable which amino acid residues would result in a peptide capable of eliciting interferon producing cells in PBL of a cancer patient that would have cytotoxic effects against survivin expressing cancer cell lines, or that would correlate to a naturally processed epitope on a cancer cell *in situ*. Even if there were factual evidence that patients with melanoma or any other cancer or pathological condition could produce a peptide-specific immune response to the claimed peptide in a pharmaceutical composition, there is no factual evidence that the patient's condition would clinically improve, *i.e.*, be 'treated', nor that a vaccine comprising the peptide could prevent a cancer. Based upon the teachings of the evidentiary references cited herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific anti-tumor effect.

Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy and in the prediction of epitope peptides from undisclosed or partially disclosed "survivin" sequences, in the absence of sufficient exemplification and guidance, one skilled in the art cannot practice the claimed method with a reasonable expectation of success. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-7, 14-17, 20-28 and 32-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 1 is indefinite in the recitation of "as determined by the assembly binding assay as described herein" because it is not clear what is meant.

b. Claim 20 is indefinite in the recitation of "A peptide ...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table" because it is not clear what is meant, *i.e.,* if the peptide has to have the amino acid residues at the positions indicated in the table or not.

c. Claim 24 is indefinite in the recitation of "the breast cancer cell line MCF-7 and the melanoma cell line FM3" because their characteristics are not known. The use of "MCF-7 and FM3" as the sole means of identifying the claimed cell lines renders the claim indefinite because "MCF-7 and FM3" is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designations to define completely distinct cell lines.

d. Claim 27 is indefinite in the recitation of "peptide...having the sequence contained in SEQ ID NO: 36....peptide having the sequence contained in SEQ ID NO: 14" because it is not clear what is meant, *i.e.,* if the peptide has the entire sequence consisting of the sequence that is the SEQ ID NO, or if the peptide has a subsequence of the SEQ ID NO.

e. Claims 36 and 37 are indefinite in the recitation of "diagnosis of the presence in a cancer patient of survivin reactive T cells" because it is not clear what is meant, *i.e,* if detection is meant.

15. For the purpose of prior art rejections, the filing date of the instant claims 1-7, 14-17, 20-28 and 32-40 is deemed to be the filing date of the 10/354,090 parent application, *i.e.,* 1/30/03, as the parent provisional application 60/352,284 does not support the claimed limitations of the instant application. It is noted by the Examiner, that although SEQ ID NO: 1-5 are disclosed in the said provisional parent application, the limitations of claim 1 are not.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-7, 14-17, 20-24, 36 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) as evidenced by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

Andersen *et al* teach the human survivin peptides with the sequences STFKNWPFL (does not bind to HLA-A2.1), FLKLDRERA (30 uM), TLPPAWQPFL (30 uM), ELTLGEFLKL (10 uM), LLLGEFLKL (1 uM, substitution analog peptide), and LMLGEFLKL (1 uM, substitution analog peptide), that correspond to SEQ ID NO: 14, 1, 2, 3, 4 and 5 of the instant claims, respectively. Andersen *et al* further teach that these peptides have *C50* (uM) values as determined in an assembly assay for peptide binding to HLA-A2.1 molecules as indicated above. Andersen *et al* teach that a CLL cancer patient's IFN-γ producing PBL responded strongly against the analog peptide LMLGEFLKL at 35 per 10^4 cells in an ELISPOT assay (see entire reference, especially Table 1 and Results).

Evidentiary reference Andersen *et al* (2001) teach the human servivin peptides ELTLGEFLKL (SEQ ID NO: 3 of the instant claims) and the substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* could exhibit cytotoxicity against the) HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3 (see entire reference, especially results).

Claims 38-40 are included in this rejection because the art reference teaches complexes of the survivin HLA-A2-binding peptides with HLA-A2.1, and wherein the HLA/peptide complexes are contacting a T cell, they are multimeric. The instant claims do not recite wherein the complex is isolated.

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Claim 20 is included in this rejection because claim 20 recites a "peptide...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following

table" and thus the V at P6 in the HLA-A2 binding motif does not have to be present in the peptide.

18. Claims 1-7, 14-17, 20-24, 36 and 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

Andersen *et al* teach the human servivin peptides ELTLGEFLKL (SEQ ID NO: 3 of the instant claims) and the substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* exhibit cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach the survivin LTLGEFLKL nonamer peptide (see entire reference, especially results).

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Claim 20 is included in this rejection because claim 20 recites a "peptide...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table" and thus the V at P6 in the HLA-A2 binding motif does not have to be present in the peptide.

19. Claims 1-7, 14-17, 20-24, 36, 38-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmitz *et al* (Cancer Res. 2000, 60: 4845-4849, IDS reference) as evidenced by Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference).

Schmitz *et al* teach the human servivin peptides ELTLGEFLKL and TLPPAWQPFL (SEQ ID NO: 3 and 2, respectively, of the instant claims). Schmitz *et al* teach that both peptides bind to HLA-A2 in an HLA stabilization assay after loading onto T2 cells, induce CD8+ effector cells when presented on DCs, and CTL of healthy donors stimulated with the peptides were able to efficiently lyse EBV-BLCLs transfected with survivin (see entire reference).

Evidentiary reference Andersen *et al* teach the human servivin peptides ELTLGEFLKL (SEQ ID NO: 3 of the instant claims) and the substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* exhibit

cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach that the ELTLGEFLKL peptide was able to induce INF-γ production from CTL from CLL patients (see entire reference, especially results).

Claim 20 is included in this rejection because claim 20 recites a "peptide...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table" and thus the V at P6 in the HLA-A2 binding motif does not have to be present in the peptide.

Claim 36 is included in this rejection because the peptides were used in solution , *i.e.,* were in a composition; the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

With regard to the inclusion of claim 24 in this rejection, although the art reference does not explicitly teach that the peptide ELTLGEFLKL is capable of eliciting INF-γ producing T cells in PBL of a patient having a cancer disease, and that these T cells have cytotoxic effect against survivin expressing cells of a cancer cell line, the art reference does teach that the peptides can stimulate CTL from PBL of healthy donors that effectively lyse a transformed B cell line, and the evidentiary reference teaches that the ELTLGEFLKL peptide was able to induce INF-γ production from CTL from CLL patients. Therefore the claimed peptide composition appears to be the same as the peptide composition of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the peptide composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 38-40 are included in this rejection because the art reference teaches complexes of the survivin HLA-A2-binding peptides with HLA-A2.1 on DCs, and wherein the HLA/peptide complexes are contacting a T cell, they are multimeric. The instant claims do not recite wherein the complex is isolated.

20. Claims 1-3, 15-17, 22-25, 28 and 32-36 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 00/03693 A1 (IDS reference).

WO 00/03693 A1 teaches vaccines that comprise an antigen that comprises one or more epitopes of survivin protein, including Class I MHC epitopes, or that comprises peptide fragments that bind to MHC class I, said vaccine in a pharmaceutically acceptable carrier, said vaccine for eliciting an antitumor immune response, including CTL response to Class I MHC epitopes, wherein the cancer patient has cancer of the colon, lung, bladder, stomach, breast, cervix, or lymphoma or leukemia, and wherein the cancer patient is human, *i.e.,* the patient has HLA class I molecules (see entire document, especially abstract, page 4 at the first four paragraphs, page 5 at the first two full paragraphs, page 6 at lines 9-21, page 11 at lines 15-30, claims, page 9 at the first two paragraphs, page 13 at lines 4-21, page 14 at lines 10-18).

Although the art reference does not explicitly teach that the epitope peptide derived from survivin either binds to Class I HLA at the *C50* value recited in instant claim 1(i) (or in claims 2 or 3), *or* is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at the recited frequency recited in instant claim 1(ii), *or* is capable of *in situ* detection in a tumor tissue of CTL that are reactive with the epitope peptide recited in instant claim 1(iii), the art reference does teach that the vaccine comprising the said peptide epitope(s) elicits an antitumor immune response to MHC class I in a human patient, so it appears that the epitope peptide is capable of *in situ* detection in a tumor tissue of CTL that are reactive with said epitope peptide. Therefore the claimed peptide composition appears to be the same as the peptide composition/vaccine of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition/vaccine of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the peptide composition/vaccine of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 17 is included in this rejection because the peptide fragment epitope(s) is/are derived from human survivin protein by deleting at least one amino acid residue from the intact protein.

Claim 36 is included in this rejection because the peptides were used in a composition; the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 1-7, 14-17, 20-25 and 36-40 are rejected under 35 U.S.C. 103(a) as being obvious over Andersen *et al* (Cancer Res. 2000, 61: 869-872, IDS reference) in view of Campbell (Monoclonal Antibody Technology. 1984, pages 1-32, Elsevier Science Publishers, Amsterdam), Harlow and Lane (Antibodies A Laboratory Manual. 1988, Cold Spring Harbor Laboratory, NY, pages 72-73) and U.S. Patent No. 6,572,864.

Andersen *et al* teach the human survivin peptides with the sequences STFKNWPFL (does not bind to HLA-A2.1), FLKLDRERA (30 uM), TLPPAWQPFL (30 uM), ELTLGEFLKL (10 uM), LLLGEFLKL (1 uM, substitution analog peptide), and LMLGEFLKL (1 uM, substitution analog peptide), that correspond to SEQ ID NO: 14, 1, 2, 3, 4 and 5 of the instant claims, respectively. Andersen *et al* further teach that these peptides have *C50* (uM) values as determined in an assembly assay for peptide binding to HLA-A2.1 molecules as indicated above. Andersen *et al* teach that a CLL cancer patient's IFN-γ producing PBL responded strongly against the analog peptide LMLGEFLKL at 35 per 10^4 cells in an ELISPOT assay (see entire reference, especially Table 1 and Results).

Andersen *et al* do not teach wherein the peptide is present in a pharmaceutical composition (claim 25), nor in a kit (claim 37).

Campbell teaches that it is routine for any group working on a macromolecule to both clone the gene coding for it and to make monoclonal antibodies to it, sometimes without a clear objective as for their application, and a method for injecting mice with a composition comprising antigen followed by hybridoma production (especially page 29 at section 1.3.4 and page 3).

Harlow and Lane teach using both bacterially produced immunogens and peptides to produce monoclonal antibodies to a protein, and that both have advantages (pages 72-73).

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes in a suitable diluent such as saline or water or adjuvants, and preparing the peptides or analogs thereof in a kit, alone or in combinations with other reagents for use in immunoassay or for use in a pharmaceutical composition (especially column 12 at lines 6-25, and column 21 at lines 44-65).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptide(s) taught by Andersen *et al* in the pharmaceutical compositions taught by Harlow and Lane and Campbell and disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make monoclonal antibodies to survivin, because Campbell teaches it is routine to make monoclonal antibodies against a macromolecule even without a clear objective for their application, Harlow and Lane teach using both peptides as well as proteins to make monoclonal antibodies against a protein, and U.S. Patent No. 6,572,864 discloses formulating peptide immunogens in pharmaceutically acceptable carriers.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide(s) taught by Andersen *et al* or composition comprising the peptide(s) taught by the combined references in a kit form as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for convenience of use because U.S. Patent No. 6,572,864 discloses putting peptide immunogens in a kit.

Claims 38-40 are included in this rejection because the primary reference teaches complexes of the survivin HLA-A2-binding peptides with HLA-A2.1, and wherein the HLA/peptide complexes are contacting a T cell, they are multimeric. The instant claims do not recite wherein the complex is isolated.

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Claim 20 is included in this rejection because claim 20 recites a "peptide...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table" and thus the V at P6 in the HLA-A2 binding motif does not have to be present in the peptide.

23. Claims 1-7, 14-17, 20-25 and 36-40 are rejected under 35 U.S.C. 103(a) as being obvious over Andersen *et al* (Cancer Res. 2001, 61: 5964-5968, IDS reference) in view of Campbell (Monoclonal Antibody Technology. 1984, pages 1-32, Elsevier Science Publishers, Amsterdam), Harlow and Lane (Antibodies A Laboratory Manual. 1988, Cold Spring Harbor Laboratory, NY, pages 72-73) and U.S. Patent No. 6,572,864.

Andersen *et al* teach the human servivin peptides ELTLGEFLKL (SEQ ID NO: 3 of the instant claims) and the substitution analog peptide LMLGEFLKL (SEQ ID NO: 5 of the instant claims). Andersen *et al* teach that HLA-A2/peptide complexes were multimerized, that the LMLGEFLKL peptide could be used to isolate and stimulate CTL that produce INF-γ, and that these CTL could lyse (*i.e.,* exhibit cytotoxicity against) the HLA-A2 positive breast cancer cell line MCF-7 and the HLA-A2-positive melanoma cell line FM3. Andersen *et al* also teach the survivin LTLGEFLKL nonamer peptide (see entire reference, especially results).

Andersen *et al* do not teach wherein the peptide is present in a pharmaceutical composition (claim 25), nor in a kit (claim 37).

Campbell teaches that it is routine for any group working on a macromolecule to both clone the gene coding for it and to make monoclonal antibodies to it, sometimes without a clear objective as for their application, and a method for injecting mice with a composition comprising antigen followed by hybridoma production (especially page 29 at section 1.3.4 and page 3).

Harlow and Lane teach using both bacterially produced immunogens and peptides to produce monoclonal antibodies to a protein, and that both have advantages (pages 72-73).

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes in a suitable diluent such as saline or water or adjuvants, and preparing the peptides or analogs thereof in a kit, alone or in combinations with other reagents for use in immunoassay or for use in a pharmaceutical composition (especially column 12 at lines 6-25, and column 21 at lines 44-65).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptide(s) taught by Andersen *et al* in the pharmaceutical compositions taught by Harlow and Lane and Campbell and disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make monoclonal antibodies to survivin, because Campbell teaches it is routine to make monoclonal antibodies against a macromolecule even without a clear objective for their application, Harlow and Lane teach using both peptides as well as proteins to make monoclonal antibodies against a protein, and U.S.

Patent No. 6,572,864 discloses formulating peptide immunogens in pharmaceutically acceptable carriers.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide(s) taught by Andersen *et al* or composition comprising the peptide(s) taught by the combined references in a kit form as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for convenience of use because U.S. Patent No. 6,572,864 discloses putting peptide immunogens in a kit.

Claim 36 is included in this rejection because the peptides were used in solution when added to the ELISPOT wells, *i.e.,* were in a composition that was used for *ex vivo* detection or diagnosis of the presence in a cancer patient of survivin reactive T cells among PBL. In addition, the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

Claim 20 is included in this rejection because claim 20 recites a "peptide...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table" and thus the V at P6 in the HLA-A2 binding motif does not have to be present in the peptide.

24. Claims 1-7, 14-17, 20-25 and 36-40 are rejected under 35 U.S.C. 103(a) as being obvious over in view of Schmitz *et al* (Cancer Res. 2000, 60: 4845-4849, IDS reference) in view of Campbell (Monoclonal Antibody Technology. 1984, pages 1-32, Elsevier Science Publishers, Amsterdam), Harlow and Lane (Antibodies A Laboratory Manual. 1988, Cold Spring Harbor Laboratory, NY, pages 72-73) and U.S. Patent No. 6,572,864.

Schmitz *et al* teach the human servivin peptides ELTLGEFLKL and TLPPAWQPFL (SEQ ID NO: 3 and 2, respectively, of the instant claims). Schmitz *et al* teach that both peptides bind to HLA-A2 in an HLA stabilization assay after loading onto T2 cells, induce CD8+ effector cells when presented on DCs, and CTL of healthy donors stimulated with the peptides were able to efficiently lyse EBV-BLCLs transfected with survivin (see entire reference).

Schmitz *et al* do not teach wherein the peptide is present in a pharmaceutical composition (claim 25), nor in a kit (claim 37).

Campbell teaches that it is routine for any group working on a macromolecule to both clone the gene coding for it and to make monoclonal antibodies to it, sometimes without a clear objective as for their application, and a method for injecting mice with a composition comprising antigen followed by hybridoma production (especially page 29 at section 1.3.4 and page 3).

Harlow and Lane teach using both bacterially produced immunogens and peptides to produce monoclonal antibodies to a protein, and that both have advantages (pages 72-73).

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes in a suitable diluent such as saline or water or adjuvants, and preparing the peptides or analogs thereof in a kit, alone or in combinations with other reagents for use in immunoassay or for use in a pharmaceutical composition (especially column 12 at lines 6-25, and column 21 at lines 44-65).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the peptide(s) taught by Schmitz *et al* in the pharmaceutical compositions taught by Harlow and Lane and Campbell and disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make monoclonal antibodies to survivin, because Campbell teaches it is routine to make monoclonal antibodies against a macromolecule even without a clear objective for their application, Harlow and Lane teach using both peptides as well as proteins to make monoclonal antibodies against a protein, and U.S. Patent No. 6,572,864 discloses formulating peptide immunogens in pharmaceutically acceptable carriers.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide(s) taught by Schmitz *et al* or composition comprising the peptide(s) taught by the combined references in a kit form as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for convenience of use because U.S. Patent No. 6,572,864 discloses putting peptide immunogens in a kit.

Claim 20 is included in this rejection because claim 20 recites a "peptide...comprising, for each specific HLA allele, any of the amino acid residues as indicated in the following table" and thus the V at P6 in the HLA-A2 binding motif does not have to be present in the peptide.

Claim 36 is included in this rejection because the peptides were used in solution , *i.e.,* were in a composition; the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition. With regard to the inclusion of claim 24 in this rejection, although the art reference does not explicitly teach that the peptide ELTLGEFLKL is capable of eliciting INF-γ producing T cells in PBL of a patient having a cancer disease, and that these T cells have cytotoxic effect against survivin expressing cells of a cancer cell line, the art reference does teach that the peptides can stimulate CTL from PBL of healthy donors that effectively lyse a transformed B cell line. Therefore the claimed peptide composition appears to be similar to the peptide composition of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the peptide composition of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 38-40 are included in this rejection because the art reference teaches complexes of the survivin HLA-A2-binding peptides with HLA-A2.1 on DCs, and wherein the HLA/peptide complexes are contacting a T cell, they are multimeric. The instant claims do not recite wherein the complex is isolated.

25. Claims 1-3, 14-17, 22-25 and 32-37 are rejected under 35 U.S.C. 103(a) as being obvious over WO 00/03693 A1 (IDS reference) in view of U.S. Patent No. 6,572,864.

WO 00/03693 A1 teaches vaccines that comprise an antigen that comprises one or more epitopes of survivin protein, including Class I MHC epitopes, or that comprises peptide fragments that bind to MHC class I, said vaccine in a pharmaceutically acceptable carrier, said vaccine for eliciting an antitumor immune response, including CTL response to Class I MHC epitopes, wherein the cancer patient has cancer of the colon, lung, bladder, stomach, breast, cervix, or lymphoma or leukemia, and wherein the cancer patient is human, *i.e.,* the patient has HLA class I molecules (see entire document, especially abstract, page 4 at the first four paragraphs, page 5 at the first two full paragraphs, page 6 at lines 9-21, page 11 at lines 15-30, claims, page 9 at the first two paragraphs, page 13 at lines 4-21, page 14 at lines 10-18).

WO 00/03693 A1 (IDS reference) does not teach wherein the peptide is present in a kit (claim 37).

U.S. Patent No. 6,572,864 discloses formulating peptide epitopes in a suitable diluent such as saline or water or adjuvants, and preparing the peptides or analogs thereof in a kit, alone or in combinations with other reagents for use in immunoassay or for use in a pharmaceutical composition (especially column 12 at lines 6-25, and column 21 at lines 44-65).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have put the peptide(s) taught WO 00/03693 A1 in a kit form as disclosed by U.S. Patent No. 6,572,864.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this for convenience of use because U.S. Patent No. 6,572,864 discloses putting peptide immunogens in a kit.

26. Claims 1-6, 14-17, 20-25 and 32-36 are rejected under 35 U.S.C. 103(a) as being obvious over WO 00/03693 A1 (IDS reference) in view of Rammensee *et al* (MHC Ligands and Peptide Motifs. Springer, Landes Bioscience, USA, pages 217-228 and 237-243, 1997).

WO 00/03693 A1 teaches vaccines that comprise an antigen that comprises one or more epitopes of survivin protein, including Class I MHC epitopes, or that comprises peptide fragments that bind to MHC class I, said vaccine in a pharmaceutically acceptable carrier, said vaccine for eliciting an antitumor immune response, including CTL response to Class I MHC epitopes, wherein the cancer patient has cancer of the colon, lung, bladder, stomach, breast, cervix, or lymphoma or leukemia, and wherein the cancer patient is human, *i.e.,* the patient has HLA class I molecules (see entire document, especially abstract, page 4 at the first four paragraphs, page 5 at the first two full paragraphs, page 6 at lines 9-21, page 11 at lines 15-30, claims, page 9 at the first two paragraphs, page 13 at lines 4-21, page 14 at lines 10-18).

WO 00/03693 A1 (IDS reference) does not teach wherein the peptide is restricted by HLA-A2, nor wherein said peptide is a nonamer or decamer peptide, nor wherein the peptide comprises any of the amino acid residues recited in instant claim 20, nor wherein the peptide is capable of eliciting INF-g producing cells in a PBL population of a cancer patient at the frequency recited in instant claim 21.

Rammensee *et al* teach predictive methods for selecting candidate HLA-A2 binding peptides, *i.e.,* motifs for peptides that bind to HLA-A2 and a length of 8-11 amino acid residues, and for epitope prediction. Rammensee *et al* teach that the motif amino acid residues for HLA-A2 binding peptides are: L or M at position 2 of the peptide and V or L at the carboxy terminal position of the peptide (see pages 217-228 and 237-243).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have scanned the sequence of *survivin* protein taught by WO 00/03693 A1 for subsequences that bind to the MHC class I molecule HLA-A2 taught by Rammensee *et al* using the predictive methods taught by Rammensee *et al* and to have made synthetic peptide versions of the subsequences as taught by Rammensee *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to select candidate peptides for HLA-A2 as per the teaching of Rammensee *et al* to test for potential use in the compositions taught by WO 00/03693 A1.

Although the art reference does not explicitly teach that the epitope peptide derived from survivin either binds to Class I HLA at the *C50* value recited in instant claim 1(i) (or in claims 2 or 3), *or* is capable of eliciting INF-γ producing cells in a PBL population of a cancer patient at the recited frequency recited in instant claim 1(ii), *or* is capable of *in situ* detection in a tumor tissue of CTL that are reactive with the epitope peptide recited in instant claim 1(iii), the primary reference does teach that the vaccine comprising the said peptide epitope(s) elicits an antitumor immune response to MHC class I in a human patient, so it appears that the epitope peptide is capable of *in situ* detection in a tumor tissue of CTL that are reactive with said epitope peptide. Therefore the claimed peptide composition appears to be similar to the peptide composition/vaccine of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition/vaccine of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the peptide composition/vaccine of the instant invention and that of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim 17 is included in this rejection because the peptide fragment epitope(s) is/are derived from human survivin protein by deleting at least one amino acid residue from the intact protein.

Claim 36 is included in this rejection because the peptides were used in a composition; the intended use of the composition comprising the peptide "for *ex vivo* or *in situ* diagnosis" recited in the said claims does not carry patentable weight *per se*, and the claims read on the active or essential ingredients of the composition.

27. Claim 38 is objected to because of the following informality: there is a spelling error, *i.e.*, "claims 1" should be "claim 1". Appropriate correction is required.

28. No claim is allowed.

29. The reference "4" crossed out in Applicant's Form 1449 filed 8/24/04 has not been considered by the Examiner because it can not be located in the parent application.

30. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
March 16, 2007

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 10/715,417	Straten and Andersen	
	Examiner Marianne DiBrino	Art Unit 1644	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Applicant is required to provide SEQ ID NO for the sequences disclosed in the instant specification on page 7 at lines 3-4.

Applicant Must Provide:

☒ ~~An initial or~~ substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ ~~An initial or~~ substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
PatentIn Software Program Support
Technical Assistance.....703-287-0200
To Purchase PatentIn Software.....703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY